



UNITED STATES DEPARTMENT OF COMMERCE  
Patent and Trademark Office

**NOTICE OF ALLOWANCE AND ISSUE FEE DUE**

HM22/0623

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HAMILTON BROOK SMITH & REYNOLDS  
TWO MILITIA DRIVE  
LEXINGTON MA 02421-4799

APPLICATION NO.	FILING DATE	TOTAL CLAIMS	EXAMINER AND GROUP ART UNIT	DATE MAILED
09/103,543	10/30/98	020	FITZGERALD, D	1646 06/23/99
First Named Applicant	LIN, 35 USC 154(b) term ext. = 0 Days.			

TITLE OF INVENTION  
MODULATION OF TGF-BETA BY TGF-BETA TYPE III RECEPTOR POLYPEPTIDES  
(AS AMENDED)

ATTY'S DOCKET NO.	CLASS-SUBCLASS	BATCH NO.	APPLN. TYPE	SMALL ENTITY	FEE DUE	DATE DUE
1	WHI91-09FXA	424-085.100	U95 UTILITY	NO	\$1210.00	09/23/99

**THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED.**

**THE ISSUE FEE MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED.**

**HOW TO RESPOND TO THIS NOTICE:**

**I. Review the SMALL ENTITY status shown above.**

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:

- A. If the status is changed, pay twice the amount of the FEE DUE shown above and notify the Patent and Trademark Office of the change in status, or
- B. If the status is the same, pay the FEE DUE shown above.

If the SMALL ENTITY is shown as NO:

- A. Pay FEE DUE shown above, or
- B. File verified statement of Small Entity Status before, or with, payment of 1/2 the FEE DUE shown above.

**II. Part B-Issue Fee Transmittal should be completed and returned to the Patent and Trademark Office (PTO) with your ISSUE FEE. Even if the ISSUE FEE has already been paid by charge to deposit account, Part B Issue Fee Transmittal should be completed and returned. If you are charging the ISSUE FEE to your deposit account, section "4b" of Part B-Issue Fee Transmittal should be completed and an extra copy of the form should be submitted.**

**III. All communications regarding this application must give application number and batch number. Please direct all communications prior to issuance to Box ISSUE FEE unless advised to the contrary.**

**IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.**

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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
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09/183,543 10/30/98 LIN

H WHI91-09FXA

HM22/0623

PATRICIA GRANAHAN  
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TWO MILITIA DRIVE  
LEXINGTON MA 02421-4799

EXAMINER

FITZGERALD, D

ART UNIT

PAPER NUMBER

1646

DATE MAILED:

13  
06/28/99

06/21  
D

This is a communication from the examiner in charge of your application.  
COMMISSIONER OF PATENTS AND TRADEMARKS

NOTICE OF ALLOWABILITY

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance and Issue Fee Due or other appropriate communication will be mailed in due course.

- ☒ This communication is responsive to Interviews 11, 17 June 1999
- ☒ The allowed claim(s) is/are 25, 31-49; to issue as 1, 3, 5, 7, 2, 4, 6, 8, 9, 11, 13, 15, 10, 12, 14, 16-20, respectively.
- ☐ The drawings filed on \_\_\_\_\_ are acceptable.
- ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- ☐ All ☐ Some ☐ None of the CERTIFIED copies of the priority documents have been
- ☐ received.
- ☐ received in Application No. (Series Code/Serial Number) \_\_\_\_\_
- ☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received: \_\_\_\_\_

- ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

A SHORTENED STATUTORY PERIOD FOR RESPONSE to comply with the requirements noted below is set to EXPIRE THREE MONTHS FROM THE "DATE MAILED" of this Office action. Failure to timely comply will result in ABANDONMENT of this application. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

- ☐ Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL APPLICATION, PTO-152, which discloses that the oath or declaration is deficient. A SUBSTITUTE OATH OR DECLARATION IS REQUIRED.
- ☒ Applicant MUST submit NEW FORMAL DRAWINGS
- ☒ because the originally filed drawings were declared by applicant to be informal.
- ☐ including changes required by the Notice of Draftperson's Patent Drawing Review, PTO-948, attached hereto or to Paper No. \_\_\_\_\_
- ☒ including changes required by the proposed drawing correction filed on 14 Dec 1998, which has been approved by the examiner.
- ☐ including changes required by the attached Examiner's Amendment/Comment.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the reverse side of the drawings. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftperson.

- ☐ Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Any response to this letter should include, in the upper right hand corner, the APPLICATION NUMBER (SERIES CODE/SERIAL NUMBER). If applicant has received a Notice of Allowance and Issue Fee Due, the ISSUE BATCH NUMBER and DATE of the NOTICE OF ALLOWANCE should also be included.

Attachment(s)

- ☐ Notice of References Cited, PTO-892
- ☒ Information Disclosure Statement(s), PTO-1449, Paper No(s) 7
- ☐ Notice of Draftperson's Patent Drawing Review, PTO-948
- ☐ Notice of Informal Patent Application, PTO-152
- ☒ Interview Summary, PTO-413
- ☒ Examiner's Amendment/Comment
- ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material

## EXAMINER'S AMENDMENT

An Examiner's Amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 C.F.R. § 1.312. To ensure consideration of such an amendment, it **MUST** be submitted no later than the payment of the Issue Fee. Authorization for this Examiner's Amendment was given in telephone interviews with Anne Collins on 11 and 17 June 1999.

## In the specification:

Page 6, line 25, following "Collection," insert:

- , 10801 University Boulevard, Manassas, VA 20110-2209 - .

Page 29, lines 6-7:

following the sequence of 'Peptide I' insert - (SEQ ID NO: 1) - ✓

following the sequence of 'Peptide II' insert - (SEQ ID NO: 2) - ✓

following the sequence of 'Peptide III' insert - (SEQ ID NO: 3) - ✓

following the sequence of 'Peptide IV' insert - (SEQ ID NO: 4) - ✓

Claim 32, at the end of indent "a," replace "or" with - and - .

Rewrite claims 38 and 39:

38.9 A method of modulating the effects of TGF- $\beta$  in a mammal, comprising administering to the mammal a polypeptide comprising the extracellular domain of a mammalian TGF- $\beta$  type III receptor wherein the mammalian receptor has an amino acid sequence selected from the group consisting of:

- a) the amino acid sequence of the TGF- $\beta$  type III receptor protein of SEQ ID NO: 6 [~~or~~] and
- b) the amino acid sequence encoded by a mammalian DNA which hybridizes to the complement of SEQ ID NO: 5 under high stringency conditions,

wherein the polypeptide specifically binds to TGF- $\beta$  under conditions appropriate for the binding of the TGF- $\beta$  type III receptor to TGF- $\beta$ , and

wherein the polypeptide is administered to the mammal in sufficient quantity to alter the level of TGF- $\beta$  binding to endogenous TGF- $\beta$  type II receptors, type III receptors, or both.

39. A method of modulating the effects of TGF- $\beta$  in a mammal, comprising administering to the mammal a polypeptide comprising the extracellular domain of a mammalian TGF- $\beta$  type III receptor wherein the mammalian receptor has an amino acid sequence encoded by:

- a) the cDNA insert contained in the plasmid deposited under ATCC accession number 75127 or
- b) a cDNA molecule which hybridizes under high stringency conditions with the complement of the coding sequence of the cDNA insert of (a),

wherein the polypeptide specifically binds to TGF- $\beta$  under conditions appropriate for the binding of the TGF- $\beta$  type III receptor to TGF- $\beta$ , and

wherein the polypeptide is administered to the mammal in sufficient quantity to alter the level of TGF- $\beta$  binding to endogenous TGF- $\beta$  type II receptors, type III receptors, or both.

- 20 **Claim 40**, at the end of indent "a," replace "or" with - and - .
- Claim 41**, indent "b," following "hybridizes," insert - under high stringency conditions - .
- Add new claims 46-49:**

46.17 A method of modulating the effects of TGF- $\beta$  in a mammal, comprising administering to the mammal a preparation consisting essentially of TGF- $\beta$  and a polypeptide comprising the extracellular domain of a mammalian TGF- $\beta$  type III receptor, wherein the mammalian receptor has an amino acid sequence selected from the group consisting of:

- a) the amino acid sequence of the TGF- $\beta$  type III receptor protein of SEQ ID NO: 6 and

601

b) the amino acid sequence encoded by a mammalian DNA which hybridizes to the complement of SEQ ID NO: 5 under high stringency conditions, and wherein the polypeptide is administered to the mammal in sufficient quantity to alter the level of TGF- $\beta$  binding to endogenous TGF- $\beta$  type II receptors, type III receptors, or both.

<sup>47.18</sup> A method according to claim <sup>17</sup>46, wherein the mammalian TGF- $\beta$  type III receptor protein has the amino acid sequence set forth in SEQ ID NO: 6.

<sup>48.19</sup> A method of modulating the effects of TGF- $\beta$  in a mammal, comprising administering to the mammal a preparation consisting essentially of TGF- $\beta$  and a polypeptide comprising the extracellular domain of a mammalian TGF- $\beta$  type III receptor, wherein the mammalian receptor has an amino acid sequence encoded by:

- a) the cDNA insert contained in the plasmid deposited under ATCC accession number 75127 or
- b) a cDNA molecule which hybridizes under high stringency conditions with the complement of the coding sequence of the cDNA insert of (a), and

wherein the polypeptide is administered to the mammal in sufficient quantity to alter the level of TGF- $\beta$  binding to endogenous TGF- $\beta$  type II receptors, type III receptors, or both.

<sup>49.20</sup> A method according to claim <sup>19</sup>48, wherein the mammalian TGF- $\beta$  type III receptor protein has the amino acid sequence encoded by the cDNA insert contained in the plasmid deposited under ATCC accession number 75127.

### REASONS FOR ALLOWANCE

The following is an Examiner's Statement of Reasons for Allowance. Any comments considered necessary by applicant must be submitted no later than the payment of the Issue Fee

and, to avoid processing delays, should preferably **accompany** the Issue Fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

By the above amendment, claims 38 and 39 are amended to adopt the binding limitation of claims 40 and 41. Claims 39 and 41 are amended to restore an inadvertently omitted requirement for high stringency hybridization, and informalities in the Markush structure of claims 38 and 40 are rectified. Claims 46-49, support for which is found in at least original claim 30, are added.

Claims 31-37 are to methods employing materials essentially corresponding to allowed composition claims in parent application serial no. 08/311,703. The instant claims employ a limitation requiring hybridization under "high stringency" conditions rather than the "stringency conditions sufficient to specifically identify said cDNA in said library." Although "high stringency" is not expressly defined in the present specification, it is a term of art which conveys a generally understood range of physical conditions and selectivity. High stringency hybridization is exemplified in the disclosure for the specific identification of TGF- $\beta$  type III receptor clones in a rat fibroblast cDNA library using a partial cDNA (R3-OF); see the specification at the paragraph bridging pages 25-26.

In the disclosure statement filed 28 January 1999, applicant has cited all of the references cited by applicant and the PTO during the prosecution of the '703 application. The instant claims patentably define over the prior art of record in this and the '703 application at least for the same reasons as do the claims in that application. *In re Ochiai*, 71 F.3d 1565, 37 U.S.P.Q.2d 1127 (Fed. Cir. 1995). In particular, the instant claims require compositions "consisting essentially of" the recited TGF- $\beta$  type III receptor polypeptides. This limitation in the claims of the '703 application was considered by the PTO to require a degree of purity which patentably distinguishes over the soluble type III receptor preparations known in the art at the time of the invention. New claims 46-49 employ the same "consisting essentially of" limitation and likewise define over the prior art.

Claims 38-45 are patentable over the prior art by virtue of the requirement that the receptor polypeptides specifically bind to TGF- $\beta$  under appropriate conditions. The soluble betaglycan (= type III receptor) proteins known in the prior art could only be detected as covalent or noncovalent complexes with radiolabeled TGF- $\beta$ . See, *e.g.*, Andres *et al.* (*J. Cell Biol.*, 1989),

of record. Because the TGF- $\beta$  binding site is already occupied, such a complex is no longer capable of binding to (additional) TGF- $\beta$ . The prior art thus did not teach how to make a fraction containing a soluble polypeptide retaining the capacity to bind to TGF- $\beta$ , as required by the claims.

5 The examiner has construed the recited "mammalian receptor protein" and "mammalian DNA" to refer to native-sequence products obtainable from primary or secondary mammalian sources, *e.g.*, tissue samples, cultured cells, DNA libraries, and so forth. In a telephone conversation on 14 June 1999, applicant's representative, Anne Collins, confirmed that this construction conforms to applicant's intentions. The examiner notes that all of the claims are cast  
10 with respect to reference DNAs or proteins, but none requires any product made by a recited process involving the reference materials.

In various preliminary submissions, applicant has rectified errors and informalities in the same manner as was employed in, *e.g.*, the immediate parent application, serial no. 08/446,939. The examiner notes particularly that the correction of the type II receptor sequences is supported  
15 by the deposit of clone 3FF and the declaration evidence provided in the submission filed 14 December 1998 (Paper No. 5).

**Any inquiry concerning this communication** should be directed to David Fitzgerald, who can be reached by any of the following means:

20 Telephone (703) 308-3934

Fax

All formal papers (703) 308-4242

Informal communications (703) 308-0294

e-mail (note PTO policies below) david.fitzgerald@uspto.gov

25 Inquiries of a general nature should be directed to the Technology Center 1 receptionists at (703) 308-0196.



DAVID L. FITZGERALD

PRIMARY EXAMINER

ART UNIT 1646

30 21 June 1999

The best time to reach Examiner Fitzgerald is from 9 a.m. to 4 p.m. (Eastern). If he cannot take a call, a message may be left on his voicemail. Should attempts to reach him be unsuccessful, the acting supervisor for this Art Unit, Paula Hutzell, may be reached at (703) 308-4310.

Most official papers and all informal **communications may be submitted to the PTO by fax**. For specific policies, refer to 37 C.F.R. § 1.6 and the notice published at 1096 O.G. 30. To facilitate their receipt and handling, please —

- ♦ Call the examiner when you send an urgent communication.
- ♦ **Do not send a duplicate copy by mail or courier.**

Any Internet e-mail communications will be made of record in the application file. PTO employees cannot engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. § 122. This policy is more fully set forth in the Interim Internet Usage Policy published in the PTO's *Official Gazette* on 25 February 1997 at 1195 O.G. 89.